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ORIGINAL RESEARCH

Treatable Traits in Patients with Obstructive Lung Diseases in a Well-Established Asthma/COPD Service for Primary Care

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Purpose: The primary objective of this study was to assess the prevalence of treatable traits (TTs) in patients with obstructive lung diseases in a primary care setting and how these TTs co-occur. The secondary objective was to assess the stability of TTs and the effect of management advice on changes in traits and health outcomes.

Patients and Methods: Data from the Dutch asthma/COPD service (2007–2023) were studied retrospectively. Patients ≥18 years with asthma, COPD, or Asthma-COPD overlap (ACO) were included. The prevalence of eight TTs were assessed: 1) insufficient inhaler technique, 2) poor medication adherence, 3) blood eosinophilia, 4) smoking, 5) obesity, 6) physical inactivity, 7) reversible airflow limitation, and 8) anxiety and/or depression. The effect of management advice on TTs was evaluated for patients with a follow-up visit scheduled within 1–2 years.

Results: In total, 15246 patients (COPD n=4822; ACO n=1761, asthma n=8663) were included. The highest proportions of TTs were insufficient inhaler technique: 43.6% (95% CI: 42.9–44.4), followed by poor medication adherence: 40.3% (95% CI: 39.2–41.4) and blood eosinophilia: 36.9% (95% CI: 35.8–38.1). Overall, 83.3% of patients had ≥ 1 TTs, and 48.9% of patients ≥ 2 TTs. Among patients with blood eosinophilia, a significant reduction of the trait at follow-up (OR: 0.61, 95% CI: 0.39; 0.96) and improved health status were observed when the pulmonologist advised the general practitioner to initiate or increase the dose of ICS. No significant association was found between management advice and the exacerbation rate at follow-up.

Conclusion: The TTs assessed in this study are common in primary care patients, with nearly half of the patients showing a combination of at least two TTs. These TTs coexist in many different combinations. A personalized approach targeting these traits may be effective in achieving better control of these heterogeneous diseases.

Keywords: COPD, asthma, asthma-COPD overlap, treatable traits, precision medicine

Introduction

Most patients with obstructive lung diseases are treated by their general practitioner (GP), guided by (inter)national recommendations for the management of asthma and COPD.[1,2] In general, these recommendations imply a standard step-wise approach of treatment, based on regular monitoring of disease severity and exacerbation burden.

Nevertheless, many patients with obstructive lung disease remain uncontrolled. An online survey among 8,000 patients with active asthma from 11 European countries found that 45% of the patients had poor symptom control and 44% reported having used an oral corticosteroids course in the last year.[3] COPD exacerbation rates also remain high despite treatment, and a higher exacerbation burden has been associated with a more rapid decline in lung function.[4] Asthma and COPD continue to impose a significant socioeconomic burden on patients and healthcare systems worldwide.[1,2]

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There is a need to improve outcomes for people with obstructive lung disease. Patients with uncontrolled disease may benefit from a more personalized approach targeting specific characteristics or "traits" they exhibit that may be treatable To achieve this, a management strategy centered on the concept of "Treatable Traits" has been proposed. This approach focuses on identifying and addressing key factors driving the patient's disease (eg, symptoms, exacerbation risk, comorbidities), enabling tailored management for each individual.[5]

Prevalences of 30 treatable traits (TTs) were recently explored in the NOVELTY cohort, a large, 3-year prospective observational study in patients diagnosed with asthma, COPD or Asthma-COPD overlap (ACO) in primary care and specialised centres around the globe.[6,7] These prevalences varied by care setting. Only six traits were tightly linked with the disease label of 'asthma' (allergic and non-allergic rhinosinusitis, nasal sinus polyps and several allergies) or 'COPD' (non-reversible airflow limitation and emphysema), whereas many others occurred independent of the diagnostic label. A limitation of this study is that the traits were assessed by the attending physician, according to their own clinical experience and judgement.[7] Given the variability in TTs observed in the NOVELTY cohort, understanding their prevalence in routine clinical practice is essential. A systematic review of 11 randomized trials recently demonstrated that this TT care model decreases hospitalizations and enhances quality of life.[8]

The Asthma/COPD-service (AC-service) in the Netherlands provides a practical framework to investigate these traits in a real-world setting, offering insights that can complement the global findings. GPs in northern Netherlands have the option to refer patients with airway symptoms to the AC-service, established in 2007 through collaboration between local pulmonologists, GPs, and a primary care laboratory.[9] The AC-service database offers a unique opportunity to quantify TTs among patients with obstructive lung disease in a real-world primary care setting.

The aims of this retrospective study were (1) to assess the prevalence and the amount of overlap of TTs in a primary care population of patients with obstructive lung disease that attended the service for the first time, and (2) to study the stability of TTs and the effect of management advice on changes in traits and health status in patients with a follow-up visit.

Methods

Study Design

This retrospective study utilized data from the AC-service database. As the data were anonymized and analyzed retrospectively, ethical approval and informed consent were not required under the Dutch Medical Research Involving Human Subjects Act (WMO). This study is reported in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) statements guidelines[10] and was conducted in accordance with the Declaration of Helsinki. The setup of the study was prespecified and registered in the ENCePP register (register reference code: EUPAS105402).

Dataset

The analysis is based on data collected from 2007 to 2023 in the AC-service.[9] The AC-service functions as a supportive diagnostic- and advice centre for GPs in the northern part of the Netherlands. GPs either refer specific patients with respiratory symptoms or refer all their patients who use pulmonary related medication to the AC-service. Patients can be treatment naïve or already using inhalation medication at the time of the assessment.

Patients referred to the AC-service are requested to complete three questionnaires at home: the Clinical COPD Questionnaire (CCQ),[11] the Asthma Control Questionnaire (ACQ)[12] and a medical history questionnaire. Lung function measurements and inhalation technique assessment are performed at a laboratory. A local pulmonologist evaluates these data electronically and provides the GP with a working diagnosis and a treatment advice. The working diagnosis and advised medication are based on guidelines and clinical experience of the pulmonologists affiliated to the AC-service. Figure 1 shows an overview of the AC-service workflow.

Data from the AC-service are linked to measurements of blood eosinophil count medical data of laboratory measurements performed by CERTE laboratory for primary care.

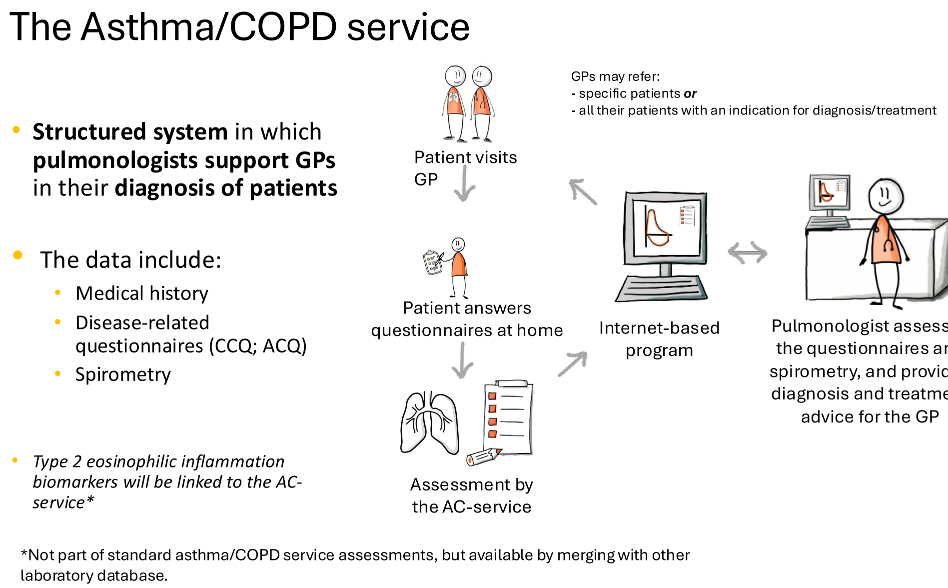

Figure 1 Overview of the Asthma/COPD-service workflow.

Study Population

For the primary objective, the study population consists of primary care patients with a working diagnosis of asthma, COPD or ACO set by a pulmonologist. We used data from patients who visited the AC-service for the first time between 2007 and 2023. For the secondary objective, patients who had a follow-up visit scheduled within 1–2 years after the first visit were included. To avoid confounding results, visits scheduled more than 2 years after the first visit were excluded, as the effect on the traits may no longer be related to the initial management advice given to the GP during the initial visit.

Health Status and Exacerbations

Questionnaires are part of the regular assessment procedure of all visits to the AC-service. As not every patient has a working diagnosis at the first visit, patients complete both the ACQ and the CCQ. These questionnaires were used to measure the asthma-related and COPD-related health status. The CCQ is a 10-item self-administered questionnaire that evaluates three domains: symptoms, functional status, and mental health.[13] The CCQ score is calculated as the average of the scores for all 10 items, each rated on a 7-point Likert scale reflecting symptom severity. The ACQ-6 is a 6-item self-administered questionnaire,[12] that assesses two domains: symptoms and medication use. The ACQ-score is derived as the average of the score for all six items, each rated on a 7-point Likert scale reflecting symptom severity. The exacerbation rate was assessed from a self-reported question: How many times in the last 12 months have you had a course (antibiotics or prednisone) for your lungs because your symptoms of cough and/or shortness of breath got worse?

Statistical Analysis

Prevalence of Trait

Descriptive statistics were used to summarize the data as means (and standard deviation, sd), medians (incl. ranges) or frequencies (incl. proportions), where appropriate. For the primary objective, the prevalence of each TT was determined by calculating the proportion (with 95% confidence intervals, 95% CI) of patients who met the pre-defined cut-off values (Table 1) at their first attendance to the AC-service divided by the total number of patients who were assessed for the first time.

Stability of Trait

For the secondary objective, the stability of each TT was assessed, with the exception of reversible airflow limitation. A trait was considered stable when it had the same status (absent or present) at the follow-up visit (1–2 years after the

Table 1 Examined Treatable Traits, Including Definitions, Cut-off Values, and Management Advice Related to Each Trait. Management Advice are Provided to the GP, with the Exception of the TTs: Insufficient Inhaler Technique and Non-Adherence to Lung Medication

#	Treatable Trait	Definition	Management Advice Related to the Treatable Trait[5]	P	S	M	H
1	**Insufficient inhaler technique**	Assessed by trained lung function analysts	Check and teach inhaler technique, or consider another device; performed at the AC-service visit^	✓	✓	X	X
2	**Poor adherence to lung medication**	Self-reported question about forgetting lung medication. Poor adherence classified as reporting to seldom or more often forgetting to take lung medication	Educate and discuss medication compliance; performed at the AC-service visit^	✓	✓	X	X
3	**Type 2 eosinophilic inflammation***	Blood eosinophil count ≥300 (cells /μL)	Initiate or increase the dose of inhaled corticosteroids, or referral to pulmonologist (for biologics)	✓	✓	✓	✓
4	**Current smoking**	Self-reported question on current smoking	Give advice to stop smoking or discuss participation to "Giving up Smoking" program	✓	✓	✓	✓
5	**Obesity**	BMI ≥30	Give dietary advice	✓	✓	✓	✓
6	**Physical inactivity**	Self-reported: "How many times a week do you exercise on a moderate intensity level for more than 30 minutes?" Trait present if answer "0 days"	Advise to improve physical fitness***	✓	✓	X	X
7	**Reversible airflow limitation****	Spirometry (post-bronchodilator): reversible airflow limitation	Treatment with bronchodilator (short- or long-acting)	✓	X	X	✓
8	**Anxiety and/or depression**	Clinical COPD Questionnaire (CCQ) – mean score mental domain ≥ 2	Discuss diagnosis and treatment of anxiety/depression[#]	✓	✓	X	X

Notes: ✓ = included in the analysis, **X** = not included in the analysis. *The blood eosinophil analysis is based on the available data collected from 2007 to 2023. The most recent available blood eosinophil data was selected for each patient. Subsequently, the eosinophil data were split into three categories using the following cut-offs: 1) <100 cells per μL; 2) 100–299 cells per μL and 3) ≥300 cells per μL.[14] **In general, reversibility tests are not performed at follow-up visits within the AC-service, only at the first visit. ***This management advice was included from 2018 onwards and data was systemically missing. ^Management advice for inhalation technique and poor adherence were consistently given at each visit if patients presented these traits, and we can therefore not assess the effect of the management advice on either the stability nor the health outcomes. [#]This management advice was systemically missing.

Abbreviations: P, prevalence; S, Stability; M, effect of management advice on stability; H, effect of management advice on health outcomes.

first visit). The distribution of changes in the status of treatable traits was visualized by Sankey diagrams for patients who had a follow-up assessment at the AC-service.

Effect of Management Advice on Stability

Multilevel mixed-effects logistic regression models were used to study the effect of management advice on the stability of the following TTs: eosinophilic inflammation, current smoking and obesity. The effect of management advice could not be assessed for all TTs (Table 1). As dependent variable, we used presence of the treatable trait (dichotomous) and as fixed effects, we included time (in months) from initial visit to follow-up visit, and whether management advice related to the trait was given at the previous assessment (dichotomous). As random effect, we included a unique identifier per pulmonologist of the AC-service that assessed the data. The association between management advice related to the trait given at the previous assessment and the presence of the trait at the follow-up assessment was estimated as an odds ratio (OR) with 95% confidence interval (CI).

Effect of Management Advice on Health Outcomes

Effects of management advice (related to the TTs: eosinophilic inflammation, reversible airflow limitation, current smoking and obesity) on health status were analysed using multilevel mixed-effects linear regression models with the

ACQ and CCQ scores as dependent variables. The results were presented as mean difference with 95% CI in ACQ/CCQ scores between patients with and without a management advice given at the first assessment. In addition, the percentage OR of patients reaching the minimal clinical important difference (MCID) for the ACQ/CCQ (ie, 0.5 and 0.4 points, respectively[15,16]) scores were reported.

Negative binomial mixed-effects models were used with the exacerbation rate in the last year as the dependent variable. The results are presented as rate ratios with 95% CI. As fixed effects, we included time (in months) between the visits as well as a variable indicating whether management advice related to the trait was given at the previous assessment. As random effect, we included a unique identifier per pulmonologist of the AC-service that assessed the data.

All analyses were checked for possible confounding (Supplementary Table 1). Each potential confounder was individually evaluated for its bias potential, defined as the change in the coefficient of the fixed effect being studied. Confounders were added to the model sequentially, starting with those having the highest bias potential. Any confounder with a bias potential of ≥5% was retained in the model.

Some patients who were assessed for the first time at the service were treatment-naïve. Sensitivity analyses were carried out to investigate potential modifying effects of having inhalation therapy prescribed prior to the first attendance of the service by including it as a fixed effect to the models, as well as an interaction term between the outcome of interest.

For the analysis, we used complete cases. The level of statistical significance was set at $p<0.05$. The sample size was determined by the number of eligible patients according to the inclusion criteria for the primary objective.

All statistical analyses were performed in R V4.4.0.[17]

Results

From the 28367 patients in the dataset, a total of 13121 were excluded. The study population therefore consisted of 15246 patients with COPD (n=4822), ACO (n=1761) or asthma (n=8663). Of these patients, 3789 patients had a follow-up visit 1–2 years after the first visit; asthma (n=2022), COPD (n=1309), ACO (n=458). Figure 2 shows a flow chart of the selection of the study population. The baseline characteristics of the study population can be found in Table 2.

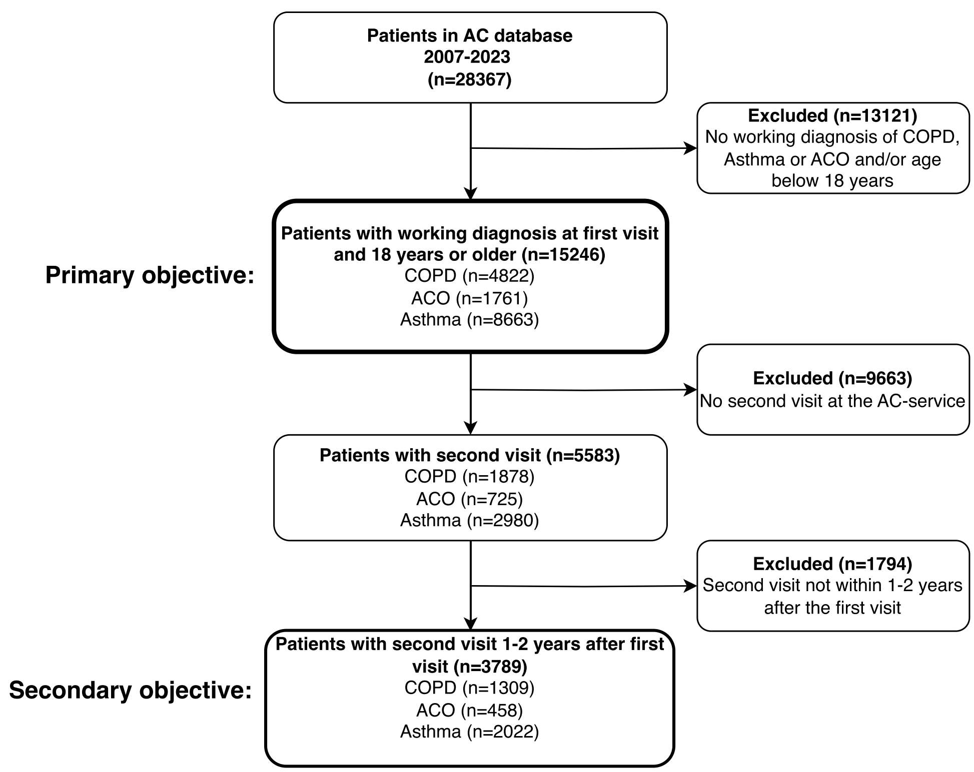

Figure 2 In- and exclusion flowchart.

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Table 2 Baseline Characteristics

	COPD (n=4822)	ACO (n=1761)	Asthma (n=8663)
Age, *mean (SD)*	65.8 (10.4)	60.3 (11.7)	47.3 (17.2)
Gender, % (n) *male*	56.2% (n=2710)	49.6% (n=873)	38.7% (n=3354)
Obesity, % (n) BMI > 30 kg/m^2	24.2% (n=1167)	28.8% (n=507)	31.0% (n=2682)
Age at which lung complaints started, *mean (SD)*	53.2 (19.2)	36.7 (23.3)	25.3 (20.4)
Smoking behavior, % (n)			
Never	3.7% (n=179)	7.8% (n=137)	45.6% (n=3947)
Former	48.3% (n=2324)	48.1% (n=846)	35.7% (n=3087)
Current	48.0% (n=2311)	44.1% (n=777)	18.7% (n=1614)
Pack years, *mean (SD)*	30.5 (20.9)	29.2 (21.2)	13.3 (14.8)
Self-reported medication regimen, % (n)			
No prescribed inhaler(s) at first visit	42.9% (n=2069)	34.0% (n=598)	35.2% (n=3049)
SABA only	11.2% (n=539)	19.5% (n=344)	22.4% (n=1944)
LAMA or LABA or ICS mono	2.2% (n=106)	2.0% (n=36)	1.3% (n=112)
LAMA+LABA	13.9% (n=648)	5.7% (n=100)	1.3% (n=111)
ICS + (LAMA or LABA)	20.3% (n=979)	30.1% (n=530)	37.9% (n=3283)
Triple therapy	9.5% (n=458)	8.7% (n=153)	1.9% (n=164)
Lung function[a], *mean (SD)*			
FEV1/FVC ratio	55.2 (11.2)	58.7 (10.0)	76.5 (8.9)
FEV1% predicted	67.8 (17.9)	71.7 (15.7)	90.4 (18.1)
Reversibility, % (n)[b]	5.8% (n=280)	31.6% (n=556)	13.7% (n=1185)
Self-reported exacerbations, %			
None in the last 12 months	60.1% (n=2899)	54.3% (n=957)	62.2% (n=5388)
At least 1 in the last 12 months	31.7% (n=1529)	34.8% (n=612)	27.7% (n=2398)
At least 2 in the last 12 months	7.8% (n=374)	9.9% (n=175)	8.9% (n=773)
Missing/Unknown	0.4% (n=20)	1.0% (n=17)	1.2% (n=104)
CCQ score, *mean (SD)*	1.10 (0.93)	1.15 (0.95)	1.07 (0.89)
ACQ score, *mean (SD)*	1.16 (0.88)	1.35 (0.93)	1.25 (0.94)

Notes: [a]Post-bronchodilator. [b]Positive bronchodilator response test defined as a reversible lung function of ≥12% and ≥200mL after administration of salbutamol and a 15-minute waiting time.

Prevalence of Treatable Traits

In the total population, the highest proportions of TTs were found for insufficient inhaler technique: 43.6% (95% CI: 42.9–44.4), followed by poor medication adherence: 40.3% (95% CI: 39.2–41.4), and blood eosinophilia: 36.9% (95% CI: 35.8–38.1) (Figure 2). There were little differences observed among the working diagnosis, except for poor medication adherence (most prominent in people with Asthma; 46.8% (95% CI: 45.2–48.4) compared to 39.7% (95% CI: 35.5–37.9) in the total population) and reversible airflow limitation (most prominent in patients with ACO; 45.1% (95% CI: 42.2–47.9) compared to 10.0% (95% CI: 9.5–10.6%) in the total population, Figure 3). In total, 83.3% of patients had ≥ 1 TTs, and 48.9% of patients had ≥ 2 TTs.

The co-occurrence of 7 treatable traits ([1] Insufficient inhaler technique [2] blood eosinophilia [3] Poor medication adherence [4] Obesity [5] Current Smoking [6] Reversible airflow limitation [7] Anxiety and/or Depression) is visualized in Figure 4. In total, complete data for the 7 TTs was available for 2139 patients (Asthma n=1212; COPD n=669; ACO n=258). In total, 225 patients (10.5%) had no TT, n=591 patients (27.6%) had 1 distinct TT, and 1323 patients (61.9%) had ≥ 2 TTs. Patients with ACO revealed more often ≥ 2 TTs (79.9%) compared to patients with Asthma (60.3%) or COPD (59.0%). The highest co-occurrence of TTs were combinations consisting of the most prevalent TTs.

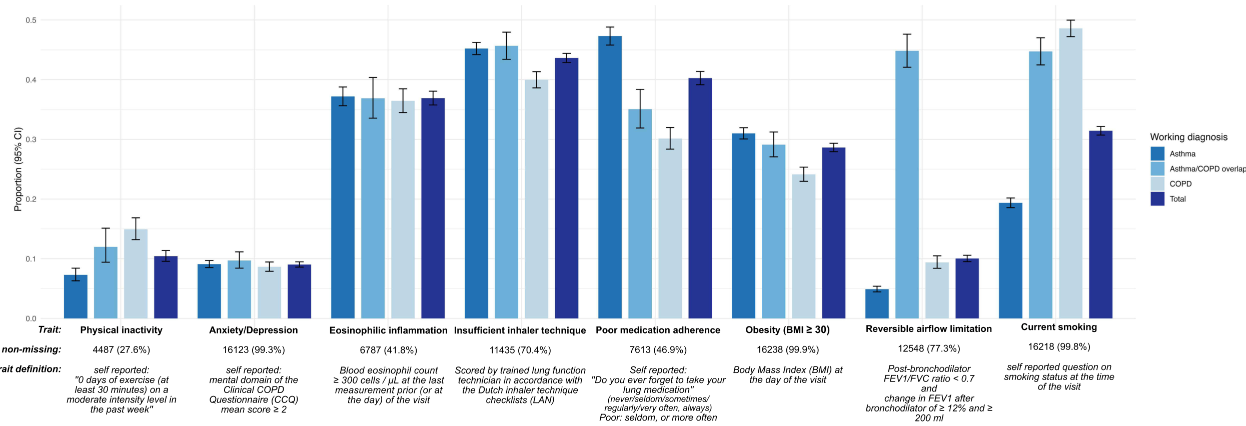

Figure 3 Proportion (95% CI) of treatable traits, stratified by working diagnosis.

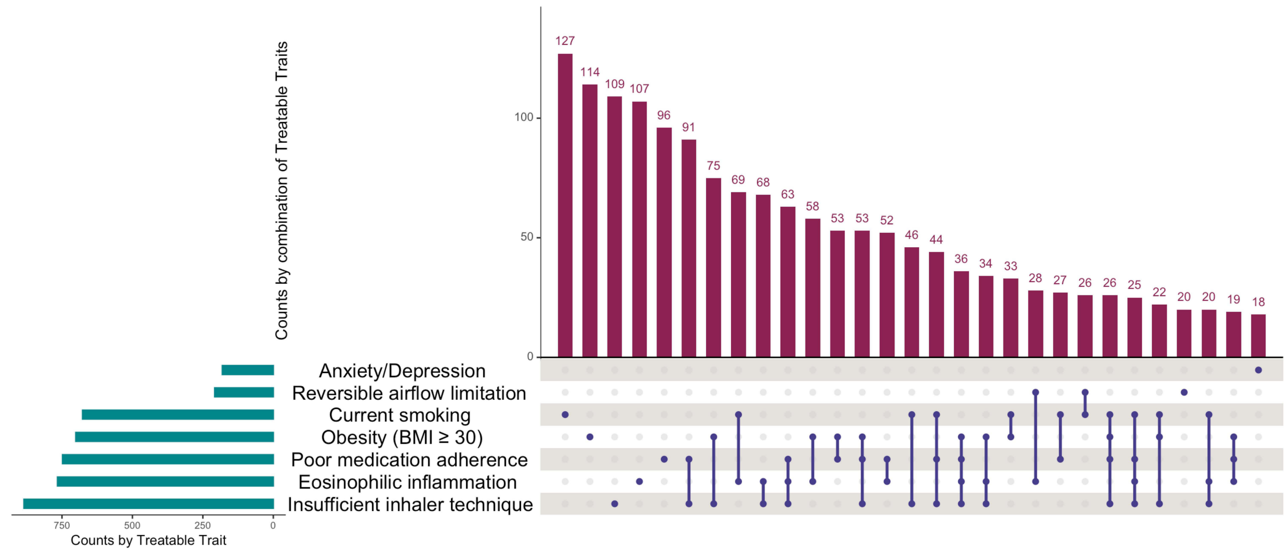

Figure 4 Overlap of treatable traits in patients diagnosed with obstructive lung disease, asthma (n=1212) COPD (n=669) and ACO (n=258). The co-occurrence and overlap of 7 TTs was studied in patients with complete data available: 1) Insufficient inhaler technique 2) blood eosinophilia 3) Poor medication adherence 4) Obesity 5) Current Smoking 6) Reversible airflow limitation 7) Anxiety and/or Depression. The lines and dots (in blue) indicate a particular pattern of (overlapping) treatable traits. The overall frequency of the distinct Treatable Traits is depicted by the green bars on the left, ordered by frequency. The numbers above the bars (in purple) indicate the number of patients exhibiting each particular pattern, ordered by frequency. Patterns of traits present in n<18 patients were excluded from this figure.

Analysis of Stability of the Traits Over Time and Effects of Given Management Advice on Changes in Traits

Patients with blood eosinophilia (prior to or at the day of the visit) were less likely to have the trait present at the follow-up visit if the management advice given to the GP was to initiate or increase the dose of ICS compared to patients who did not receive this advice (OR 0.61, 95% CI (0.39; 0.96), p=0.036), see Table 3.

Of the 1121 patients with obesity at the first visit, 10.1% (n=113) did not present the obesity trait at the follow-up visit. In the group of patients where a dietary advice was given by the pulmonologist (n=431), 4.9% of the patients did not present the obesity trait at the follow up visit, whereas in the group of patients that did not receive the advice (n=690), 13.3% did not present the obesity trait at the follow-up visit. Patients were more likely to have the trait present at the follow-up visit if the management advice given to the GP was to give a dietary advice compared to patients who did not receive this advice (OR 2.48, 95% CI (1.50; 4.08), p=0.036), see Table 3. Overall, the decrease in BMI between the first

Table 3 Effects of Management Advice, Given to the GP, on Changes in Traits From the First to the Follow-up Assessment

Treatable Traits Present at First Visit	Management Advice given to the GP at First Visit	Odds Ratio (95% CI) for Presenting the Trait at Follow-up Visit When the Advice was given to the GP
Blood eosinophilia (n=645)	Initiate or increase the dose of ICS (n=199)	0.61 (95% CI: 0.39; 0.96), p=0.036 *adjusted for age, previous ICS use*
Current Smoking (n=1038)	Patient is interested in smoking cessation program (n=109)	0.71 (95% CI: 0.42; 1.18), p=0.183 *adjusted for medication regimen*
Obesity (n=1121)	Give dietary give (n=431)	2.48 (95% CI: 1.50; 4.08), p<0.001 *adjusted for BMI at first visit, sex*

and the follow-up were relatively small; 0.01 (±1.95) kg/m^2 for those patients who received a dietary advice and 0.01 (±1.95) kg/m^2 for patients who did not receive the advice. The overall difference between the first and follow-up visit are visualized in Supplementary Figure 1.

The overall changes of TTs between the first attendance and the follow-up visit are visualized with Sankey plots and can be found in Supplementary Figures 2–8.

Association of Management Advice Given to the GP on Health Status and Exacerbation Rate

The management advice “initiate or increase the dose of ICS” was significantly associated with decreased CCQ-score (−0.20 (95% CI: −0.34; −0.07), p=0.003) and decreased ACQ-score (−0.37 (95% CI: −0.51; −0.23), p=0.001) after correcting for confounders (Figure 5). 27.6% of the patients with the advice and 20.2% of the patient without the ICS advice had an improvement in CCQ that exceeded the MCID (OR 1.51, 95% CI: 1.03–2.23). 47.7% of the participants

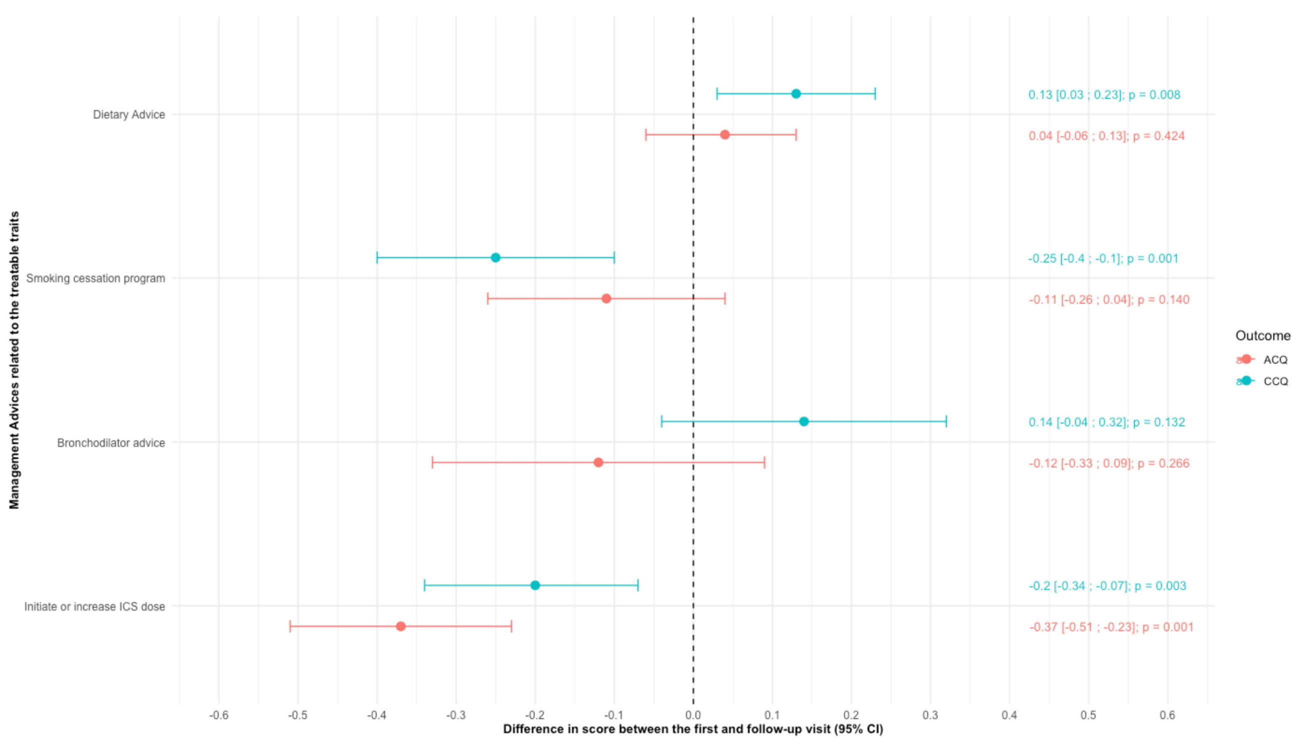

Figure 5 Associations between management advice (given to the GP) and the CCQ and ACQ.

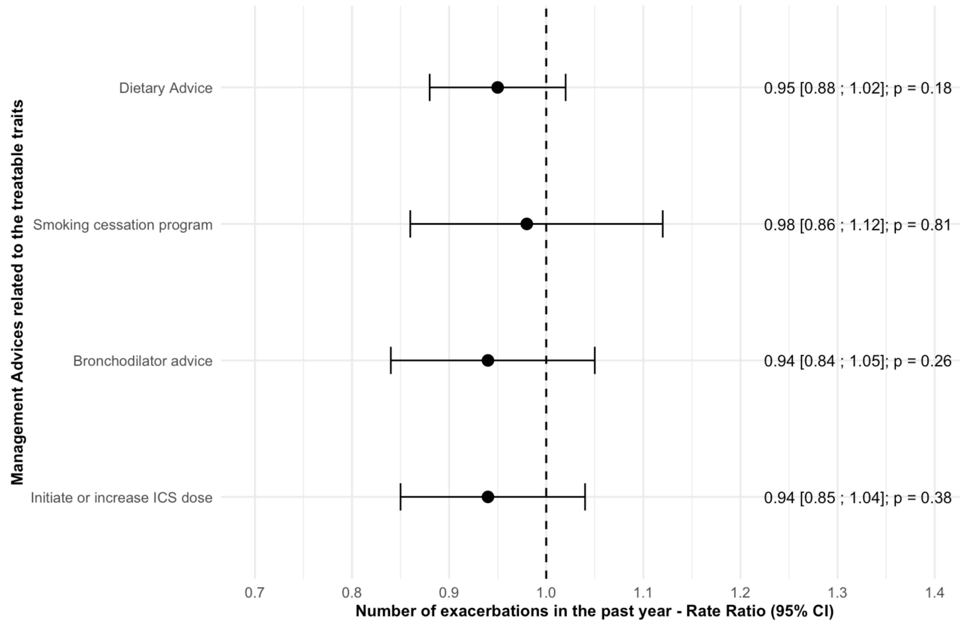

Figure 6 Associations between management advice (given to the GP) and the number of exacerbations in the past year.

with the ICS advice and 25.6% of the patient without the ICS advice had an improvement in ACQ that exceeded the MCID (OR 2.66, 95% CI: 1.87–3.78).

Patients who were interested in a smoking cessation program had significantly decreased CCQ score (−0.25 (95% CI: −0.40; −0.10), p=0.001). 39.4% of the patients who were interested in a smoking cessation program and 22.2% of the patient who were not interested had an improvement in CCQ that exceeded the MCID (OR 2.27, 95% CI: 1.50–3.44).

Patients with obesity that received the dietary advice had significantly increased CCQ-score (0.13 (95% CI 0.03–0.23), p=0.008) compared to patients who did not receive the advice. 23.7% of the participants with the dietary advice and 30.4% of the patient without the dietary advice had an improvement in CCQ that exceeded MCID (OR 0.71, 95% CI: 0.54–0.93).

No significant association was found between management advice and the exacerbation rate at follow-up (Figure 6).

Discussion

The present study investigates the prevalence and overlap of 8 TTs in primary care patients with obstructive lung disease who were assessed for the first time at the Dutch Asthma-COPD service in the Northern part of the Netherlands. Additionally, the study evaluated the stability of these traits and the effect of management advice on changes in traits and health status over a follow-up period of 1–2 years after the initial diagnostic visit. The AC-service offered a unique opportunity to quantify the prevalence and overlap of TTs in a real-world population of patients with obstructive lung disease, where most datasets focus on selected diseases.

We show that, irrespective of the ‘diagnostic label’, most patients present with at least one TT, with half of the patients presenting with two or more TTs during their first attendance at the AC-service, with various patterns of TT co-occurrence observed (Figure 4). Large variations in the presence of traits over time were observed (Supplementary Figures 2–8). These observations clearly support the need for a personalized model of care for obstructive lung diseases targeting these specific treatable traits, as has been proposed by Agusti et al (2021).[5] Moreover, our findings underscores the complexity and heterogeneity of obstructive lung diseases, extending beyond the degree of airflow limitation in for instance patients with COPD.[18] Addressing TTs in chronic conditions is important and may foster opportunities to improve patients’ health status by doing so in a timely and effective manner.

The clinical relevance of targeting TTs in primary care was shown. Management advice that were given to the GP of patients that presented with the trait at the first-attendance, particularly in relation to blood eosinophilia, decreased the likelihood of presenting the trait at the follow-up attendance and improved health status in patients with obstructive lung

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disease. No significant associations were found between specific management advice and the exacerbation rates at the follow-up visit. It is important to note here that, in general, the AC-service proved to be effective in reducing the exacerbation risk in patients with Asthma and COPD. The proportion of asthma and COPD patients with ≥1 exacerbation in the last year decreased in patients who had a yearly follow-up at the service.[9] In our updated dataset, we observed the same trend, with 23.1% of patients revealing a reduction in exacerbations during the follow-up attendance at the AC-service. Moreover, we should acknowledge that the analysis is focused on a follow-up visit 1–2 years after the initial (diagnostic-) visit. The AC-service makes a significant contribution to the diagnostic pathway for individuals with obstructive lung diseases in the area. However, particularly for changes in certain behavior-related traits, such as smoking and obesity, more consultations (ie, beyond a single treatment advice to the GP) may be necessary to drive behavior change. To support this, the implementation of more frequent telemonitoring within the AC-service, combined with educational components,[19] could be a promising addition to the service to further improve clinical outcomes. Combining these findings suggests that a personalized TT-approach, focused on the identification and targeting of clinically relevant and modifiable traits, may improve disease control in primary care of patients with obstructive lung disease.

In this study, Type 2 eosinophilic airway inflammation has been assessed by blood eosinophil counts. Eosinophilic airway inflammation is associated with an increased exacerbation risk and higher disease severity in patient with obstructive lung disease.[1,2] In Asthma, the eosinophilic phenotype is prevalent, affecting 50–70% of patients with type 2 high asthma[20] – and this prevalence rises to over 80% in patients with severe asthma.[21] In COPD, airway inflammation is generally associated with a neutrophilic response (Type 1); however, consistent with the COPD population in our study, 20–40% of patients with COPD also exhibit an eosinophilic phenotype.[20,22] Emerging evidence indicates that blood eosinophils serve as a predictive biomarker for responsiveness to ICS in asthma and COPD. For instance, higher blood eosinophil levels in COPD are associated with a reduction in exacerbation rates following ICS treatment.[23] Similarly, greater treatment benefits have been observed in patients with eosinophilic asthma treated with ICS compared to those with lower blood eosinophil count.[24] The GOLD-strategy report recommends using a blood eosinophil count of ≥ 300 cells/μL to guide the use of ICS.[2] In our study, greater treatment benefits (ie, reduction of the trait at follow-up and improved health status) were observed in patients with eosinophilic inflammation biomarkers prior to the first attendance of the AC-service, where the pulmonologist advised the GP to initiate or increase the dose of ICS, compared to patients with eosinophilic inflammation biomarkers that did not receive this advice. The management advice did not significantly reduce the exacerbation rate, however, we should acknowledge that (a) it is plausible that not all treatment recommendations were followed by the GP (ie, a previous study observed discordance between the advised inhalation medication and the patient-reported medication at the follow-up visit[25]) and (b) the eosinophilic inflammation biomarkers were not part of the standard Asthma/COPD service (Figure 1 and Table 1), and (c) the Dutch GP COPD guidelines do not yet recommend blood eosinophil count as a predictive marker of targeting ICS. In summary: blood eosinophilia is a critical TT to address, and its assessment in primary care can help guide treatment decisions.[26]

In addition to eosinophilic inflammation, the effect of AC-service management advices given to the GP on outcomes was also evaluated for the TTs: obesity, smoking and reversible airflow limitation. Notably, patients with obesity who received a dietary advice were more likely to continue presenting the trait at the follow-up visit and exhibited worse health status (higher score on CCQ) compared to patients who did not receive the advice. This finding may be partly attributed to our lack of information regarding whether the GP followed up on the treatment advice provided by the AC-service. In contrast, current smokers who expressed interest in participating in a smoking cessation program were less likely to present the trait at the follow-up visit and had a better health status compared to those who were not motivated to stop smoking at all. This finding further emphasizes the importance of psychosocial factors in the management of obstructive lung diseases, particularly when targeting extrapulmonary and behavior TTs (eg, obesity, smoking behavior, inhaler technique and medication adherence).[26]

The present study aimed to assess the prevalence and impact of TTs in a real-world population of patients, enhancing the generalizability of our findings. The high proportions of individual traits (such as insufficient inhaler technique and poor medication adherence) align with the observations from previous observational studies.[27,28] The dataset used is the result of over 17 years of data collection from a protocolled, well-established Asthma-COPD service covering an estimated 70% of the population in its operational area. A strength of this study is that data from a range of obstructive lung diseases could be included, whereas most datasets focus on a single 'diagnostic label'. In this sample, very few patients had been previously diagnosed by a specialist, as those cases typically do not require referral to the AC-service. Approximately 80% of the patients in the AC-service could be diagnosed by the system.[9] However, the effect of management advice could not be assessed for all TTs (eg, reversibility was generally evaluated only at the first diagnostic visit). Moreover, TTs such as inhaler technique and medication non-adherence were directly addressed during the visits and could therefore not be included in the data analysis regarding the effect of management advice on health outcomes (Table 1). We have demonstrated that there is considerable variation of these important traits over time (Supplementary Figures 2 and 3). Despite the exclusion of these TTs from the analyses on clinical outcomes, effectiveness trials have been conducted in other settings to explore the benefits of individualized care targeting these traits. It is important to note that the number of TTs examined in this study is not exhaustive. Other traits (eg, adherence to vaccine schedule) may also be relevant to consider in the phenotyping of patients with obstructive lung disease. We chose this specific set of TTs because evidence-based interventions are available (Table 1) and since they were captured within the AC-service.

Although our analyses were adjusted for multiple potential confounders based on literature and clinical expertise, due to the inherent heterogeneity of airways diseases, we cannot exclude residual confounding.

The current findings highlight the importance of a comprehensive assessment for each patient with obstructive lung disease early in their disease course, followed by a personalized management plan that incorporates both pharmacological and non-pharmacological treatments. A TT approach is feasible to implement and does not require extensive resources, such as validated questionnaires or inhaler technique assessments. Future research is needed to determine which key treatable traits should be prioritized in the management of obstructive lung diseases in primary care. An in-depth analysis of the clinical relevance of overlapping traits for management of obstructive lung diseases would further contribute to the evidence base for a TT model of care. Gaining more insights into the overlap of traits is relevant because traits such as insufficient inhaler technique could impact the effectiveness of inhaled medication, thereby having a (bi-directional) relationship with poor adherence to medication.

Conclusion

The burden of disease for asthma and COPD remains high because of the complexity and heterogeneity of these diseases. In this group of primary care patients with obstructive lung disease, the majority of patients show clear treatable traits. Identifying these treatable traits and targeting with tailored interventions may lead to improved disease control.

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